Early Vs. Late Androgen Deprivation:
Lessons from the Literature and the Clinical Implications

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The Modern Treatment Failure: Rising PSA

- Scope of the Problem
- Definition
- Evaluation
- Treatment
  - Local
  - Systemic
Rising PSA:
Scope of the Problem*

- Approximately 30-40% of patients will experience a rising PSA after local therapy
  - 180,400 patients diagnosed with prostate cancer in 2000
  - 2/3 (119,064) of these patients receive definitive local therapy
  - 30-40% (35,719-47,625) recur

*Based on SEER statistics. 1998
Rising PSA

• Common problem
• Definition
• Evaluation
• Treatment
  – Local
  – Systemic
Rising PSA: What is a Biochemical Recurrence?

Radical Prostatectomy

• Nadir within 2 months after surgery
• Multiple PSA “cutoffs” used to define failure

Radiotherapy

• Nadir may take 27 months to reach
• ASTRO criteria used to define failure
  • 3 consecutive rises in PSA, 6 months apart
Rising PSA:
What is a Biochemical Recurrence?

- Mayo Clinic study with 2,782 patients after RP between 1987 and 1993
- Percentage of patients with a rise in PSA within 3 years of Cut-Point

<table>
<thead>
<tr>
<th>PSA Level</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 ng/mL</td>
<td>49%</td>
</tr>
<tr>
<td>0.3 ng/mL</td>
<td>62%</td>
</tr>
<tr>
<td>0.4 ng/mL</td>
<td>72%</td>
</tr>
</tbody>
</table>

- Conclusion: PSA $\geq 0.4$ ng/mL is best level to consider biochemical failure
- ASTRO criteria favorably biases biochemical results

Rising PSA: What is a Biochemical Recurrence?

- Definition for Brachytherapy
  - 591 men treated from 1992-1996
  - T1-T2NX prostate cancer, median pretreatment PSA=7.3ng/mL
  - I-125 implant + external beam
  - PSA nadir <0.2 ng/mL – 99% 8-year disease free survival rate, only 16% if nadir 0.3-1.0ng/mL

Rising PSA: What is a Biochemical Recurrence?

- Definition for Brachytherapy
  - Substantially fewer recurrences: 65 recurrences vs. 93 recurrences, if ASTRO criteria rather than 0.2ng/mL cut point used \((p<0.0001)\)
  - Conclusion: PSA nadir should be <0.2 ng/mL
    Studies should use similar PSA criteria to compare outcomes

Rising PSA:
Definition of PSA Recurrence

- Conclusions
  - Radical Prostatectomy PSA > 0.4ng/ml
  - Radiation – three consecutive rises above a nadir (ASTRO criteria)
  - Brachytherapy – rise above a nadir of 0.2ng/mL
Rising PSA

• Common problem
• Definition
• Evaluation
• Treatment
  – Local
  – Systemic
Rising PSA: Evaluation After Local Therapy

- Factors to differentiate local vs. metastatic disease
  - Pre-Rx PSA, path. specimen (stage, grade)
  - Slope of PSA rise or PSA doubling time
  - Bone scan/CT
  - Digital Rectal Exam/Fossa biopsy
  - ProstaScint scan
  - Endorectal coil MRI, PET and SPECT scans
Rising PSA: Evaluation After Local Therapy

• Clinical factors which favor metastatic disease

  – High preoperative PSA > 20, seminal vesicle invasion, Gleason score 8-10

  – A PSA > 0.4 ng/mL in the first year

  – PSA velocity -> 0.75 ng/mL per year

  – PSA doubling time < 6 months
Rising PSA: Value of the Bone Scan

Predicted Probability of Positive Bone Scan (%)

“High Threshold”

Trigger PSA (ng/mL)
Rising PSA: Detection of Local Recurrence

- CT scan not very helpful (especially with PSA < 40)

- Digital rectal exam - not very sensitive, scarring may give false positives

- Prostatic fossa biopsy
  - Overall 50% positive
  - If PSA < 1.0 ng/mL only 25% positive
  - Multiple biopsies increase sensitivity but also patient discomfort
Rising PSA: ProstaScint Scan

- Radiolabeled monoclonal antibody to prostate-specific membrane antigen (PSMA)
  - for patients who are at high risk of lymph node metastases
  - for patients who have a rising PSA after radical prostatectomy
Rising PSA: ProstaScint

- Antibody to PSMA radiolabeled with Indium-111 and injected intravenously
- Gamma camera detects sites of antibody localization if present
Rising PSA: ProstaScint – Fossa Recurrence

- 54-year-old post-radical prostatectomy
- PSA up to 2.4 ng/mL
Rising PSA: Evaluation of ProstaScint

- 158 patients-s/p RRP (T2 or T3 disease)

- Rising PSA ± positive DRE
  - PSA <1.0 ng/mL and positive DRE, or PSA >1.0 ng/mL any DRE

- Negative or equivocal bone scan, CT/MRI

- Scheduled for fossa needle biopsy

*Moul et al.*
### Rising PSA: Evaluation of ProstaScint

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>ProstaScint +</th>
<th>ProstaScint -</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy +</td>
<td>29</td>
<td>30</td>
<td>49%</td>
<td>71%</td>
</tr>
<tr>
<td>Biopsy -</td>
<td>29</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>50%</td>
<td>Negative predictive value</td>
<td>70%</td>
<td>Overall accuracy</td>
</tr>
</tbody>
</table>

*Moul et al*
Rising PSA: PET and SPECT Scans

- **Positron emission tomography**
  - Uses 18FDG or 11C-methionine to detect increased metabolism of metastatic sites
  - 18 FDG hard to interpret because it accumulates in the urine
  - Prostate cancer often with slow growth rate and may get false negatives
- **Single photon emission computed tomography**
  - Allows more accurate localization of bone metastases
- **Endorectal coil MRI**
  - Investigational
Rising PSA:
Limitations of Localization Studies

• Conclusions
  – Currently no study reliably localizes tumor to pelvis
  – Positive study doesn’t exclude mets
Rising PSA

• Scope of the Problem
• Definition
• Evaluation
• Treatment
  – Local
  – Systemic
Rising PSA: Clinical Course

Radical prostatectomy (N=1,997 between 1982 and 1997)

PSA-only recurrence (N=315; 15%)

8 years median

Clinical metastases

5 years median

Death from prostate cancer

Rising PSA: Treatment

• Treatment options
  – Salvage XRT
  – Salvage RRP or cryotherapy (after XRT)
  – Early hormonal therapy
Rising PSA: Salvage XRT

- Predictive factors for successful salvage XRT
  - Gleason score ≤7
  - No seminal vesicle invasion
  - Undetectable post RRP nadir
  - PSA <2ng/mL preXRT treatment

Pisansky et al *J. Urol* 2000;163:845-850
### Rising PSA: Salvage XRT

Salvage Radiotherapy to the Prostatic Bed for Radical Prostatectomy PSA-Only Recurrence

<table>
<thead>
<tr>
<th>Author</th>
<th>Salvage XRT Given for PSA Above:</th>
<th>Disease-Free Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu, et al</td>
<td>2.5 ng/mL</td>
<td>8%</td>
</tr>
<tr>
<td>Schild, et al</td>
<td>1.1 ng/mL</td>
<td>26%</td>
</tr>
<tr>
<td>Forman, et al</td>
<td>2.0 ng/mL</td>
<td>33%</td>
</tr>
<tr>
<td>Zelefsky, et al</td>
<td>1.0 ng/mL</td>
<td>17%</td>
</tr>
</tbody>
</table>
Rising PSA: Salvage RRP

- 66% of patients with a positive biopsy after XRT developed clinical recurrence

- 29% with negative biopsies relapsed

- However 18% with positive biopsies did not develop clinical recurrence at 10 years

Scardino et al. J. Urol 1986
Rising PSA:
Salvage RRP

- Patients should have had localized disease prior to XRT
- Increased rate of post operative complications
  - Anastomotic strictures 10-27%
  - Rectal injuries 0-15%
  - Incontinence (severe >2 pads/day) 10-60%
  - Impotence 90-100%
Rising PSA: Salvage RRP

• Results
  – Preoperative PSA $< 10\text{ng/mL}$
    • 5 yr biochemical free survival - 50%
  – Preoperative PSA $> 10\text{ng/mL}$
    • 5 yr biochemical free survival - 29%
  – Organ confined
    • 5 yr biochemical free survival - 100%
  – Non organ confined
    • 5 yr biochemical free survival - 28-71%

Rogers et al. *J Urol* 1995
Rising PSA: Salvage RRP

• Conclusions

  - Salvage RRP after XRT best for:
    • PSA < 10ng/mL
    • Organ confined disease
    • Motivated patients with > 10 years life expectancy
Rising PSA: Salvage Cryotherapy

- 5 year follow-up in 150 patients who underwent salvage cryotherapy after XRT

- All cases biopsy proven recurrence and no clinical evidence of metastatic disease

- Overall disease free survival at 5 years was 40%

Izawa et al. *JCO* 2002: 2664
Rising PSA: Salvage Cryotherapy

• Predictors of failure
  – High pre-XRT clinical stage (>T2)
  – Pre cryotherapy PSA > 10ng/mL
  – Pre cryotherapy Gleason score ≥ 9
  – Increasing PSA despite hormonal therapy

• Complications of cryotherapy
  – Urinary incontinence rate of 6-8% in contemporary series
Conclusions

• Many PSA recurrences after definitive local therapy probably represent occult metastatic disease
NCCN Guidelines
Post-Definitive Therapy Surveillance

• PSA level checked q6 mos. X 5 years, then yearly

• 45% of PSA recurrence occurs < 2 years
  77% < 5 years
  23% > 6 years
  *Pound et al. JAMA 281:1591-97, 1999*

• Bone scans when symptoms develop or rapid rise in PSA

• Probability of positive bone scan < 5% if PSA < 40 ng/ml or
  PSA slope < 5.0 ng/ml/month
  *Cher et al. J Urol. 160:1387-91, 1998*
NCCN Guidelines
Failure of PSA to Normalize

- If + surgical margin – XRT +/- hormones
- Hormonal therapy alone less preferred
- If negative surgical margin – observation or hormonal intervention (no consensus)
NCCN Guidelines
Rising PSA

• Definitions of PSA failure vary (0.2-0.6)

• Attempts to identify local recurrence vs. distant disease have been disappointing

• CT, MRI, Prostascint, Bone scan
Rising PSA: Treatment Questions?

• Is early hormonal treatment better than later treatment?
• How does DES-5mg compare with orchiectomy and does orch+DES>orch alone?

• Results:
  a.) 5mg DES high CV toxicity
  b.) All endocrine tx, when given at diagnosis had slower disease progression in stage III and IV patients
  c.) No effect on survival in III and IV patients
  d.) DES better than orchiectomy in preventing cancer deaths
  e.) 44% of placebo arm went on to receive endocrine therapy…could infer that early therapy better than delayed
VACURG II

- Randomized 506 men in stage III and IV to either placebo vs. 0.2mg, 1.0mg and 5.0mg DES.

- DES-1.0mg = DES 5mg in delaying cancer progression

- DES-1mg given at diagnosis improved survival compared with placebo, 0.2mg and 5mg DES

- DES 1mg, early intervention recommended in younger patients with high grade tumors, but not in elderly
Stage III and IV men randomized to either Premarin 2.5mg, Provera 30mg, Provera + DES-1mg and DES-1mg alone

No difference in overall survival between groups

DES 1mg alone better than other tx in delaying progression of disease from stage III to IV

Delay in progression most pronounced in younger men (<75 years) and high grade (Gleason 7-10)

DES-1mg can still have increased CV effects in elderly or ill men
6 Conclusions from VACURG

• DES-5mg high CV toxicity profile
• Orch + DES=orch or DES alone (DES>orch in delaying progression)
• DES 1mg=DES 5mg
• Reduced CV hazard for DES-1mg
• Premarin/provera no better than DES-1mg
• VACURG studies suggest survival benefit of early vs. late therapy
Leuprolide Vs. DES

• Leuprolide Study Group: compared DES-3mg to Lupron 1mg SQ QD form men with metastatic prostate cancer

• Lupron=DES-3mg in survival and response rate

• Less side effects with leuprolide

NEJM, 311(20): 1281-1286, 1984
Rising PSA: Treatment

Trials Demonstrating a Prostate Cancer Progression/Survival Benefit for Early Hormonal Therapy

• MRC study

• Bolla study (EORTC)

• ECOG/Intergroup D1 study (Messing)

• Casodex Early Prostate Cancer Trialist Group
Rising PSA: Treatment

- **MRC Study**
  - 934 patients studied
    - 55% no metastatic disease by bone scan (M0)
    - 25% with metastatic disease (M1)
    - 20% metastatic status unknown (MX)

  - Randomized to early hormonal therapy (469 patients) vs. delayed therapy (465 patients)

  - Patients followed for progression, complications, and survival
Rising PSA: Treatment

• MRC Study-complications
  – Spinal cord compression and pathologic fractures
    • 20/469 in immediate treatment vs. 44/465 in deferred treatment
  – Patients requiring TURP
    • 65/469 in immediate vs. 141/465 in deferred treatment
  – Ureteric obstruction
    • 33/469 in immediate vs. 55/465 in deferred treatment
Rising PSA: Treatment

- MRC study-survival

![Graph showing the survival rates over time for deferred and immediate treatments with a p-value of 0.001.]
MRC Study-Survival

• Survival advantage seen in M0 patients, but not in M1/MX men

• Patients with M1/MX disease had fewer side effects with early therapy
Critique of MRC Trial

- Initially powered for 2000 men, only 938 enrolled
- Intention to treat analysis rather than a true comparison of two treatment arms
- Significant number of MX patients in which presence of mets not know
- Immediate tx = within 6 weeks
- 50% of M1 deferred arm received tx within 9 months
Goserelin Plus Radiotherapy in Locally Advanced Prostate Cancer

Patients With Stage T1 - T4 Disease

Randomize (N=415)

- external irradiation (N=208)
- external irradiation + Zoladex (N=207)

Radiation: 50 Gy over 5 weeks plus 20 Gy over 2 weeks
Zoladex: 3.6 mg SC every 4 weeks starting Day 1 of radiation for 3 yr
Cyproterone: 150 mg po qd for 1 month starting 1 week prior to zoladex

Goserelín Plus Radiotherapy in Locally Advanced Prostate Cancer

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Kaplan-Meier Estimate of the Disease-Free Interval

No. of Patients at Risk

Radiotherapy

Combined treatment

No. Who Died

Radiotherapy

Combined treatment

Kaplan-Meier Estimate of Overall Survival

P = 0.001 (overall log-rank test)

<table>
<thead>
<tr>
<th>Year</th>
<th>Radiotherapy</th>
<th>Combined treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients at Risk</td>
<td>No. Who Died</td>
</tr>
<tr>
<td>0</td>
<td>208 183 139 96 67 39 23 10 6</td>
<td>58</td>
</tr>
</tbody>
</table>

Zoladex Plus Radiotherapy in Locally Advanced Prostate Cancer

Conclusion

Adjuvant treatment with zoladex for 3 years, when started simultaneously with external irradiation, improves local control and survival in patients with locally advanced prostate cancer

Critique of EORTC Trial

• 45 months median follow up – projected survival rates are uncertain until longer follow up

• Improved effect of hormones+XRT may be cytoreductive and not have any real effect on micrometastatic disease
IMMEDIATE HORMONAL THERAPY COMPARED WITH OBSERVATION AFTER RADICAL PROSTATECTOMY AND PELVIC LYMPHADENECTOMY IN MEN WITH NODE-POSITIVE PROSTATE CANCER

Edward M. Messing, MD, Judith Manola, MS, Michael Sarosoy, MD, George Wilding, MD, E. David Crawford, MD, and Donald Trump, MD
# Rising PSA: Treatment

## Immediate Hormone Therapy vs. Observation

<table>
<thead>
<tr>
<th>Population</th>
<th>98 Men with node-positive prostate cancer s/p radical prostatectomy and pelvic lymphadenectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Randomly assigned to immediate LHRH q 28 days or bilateral orchiectomy or observation until disease progression</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Overall survival, prostate cancer-specific survival and progression-free survival</td>
</tr>
<tr>
<td>Sample</td>
<td>n=47 – immediate antiandrogen therapy, n=51 – observation</td>
</tr>
<tr>
<td>Duration</td>
<td>Median 7.1 years (3-10)</td>
</tr>
</tbody>
</table>

Rising PSA: Treatment

Results of Immediate Hormone Therapy vs. Observation

- N=98; 1988-1992
- Mean follow-up: 7.2 years

<table>
<thead>
<tr>
<th></th>
<th>IHT</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death-PC</td>
<td>4.3%</td>
<td>30.8%</td>
</tr>
<tr>
<td>Progression</td>
<td>18.8%</td>
<td>75.0%</td>
</tr>
</tbody>
</table>

Progression-Free Survival

NO. AT RISK

<table>
<thead>
<tr>
<th></th>
<th>Immediate therapy</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>47</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

P < 0.001
Overall Survival

![Graph showing Overall Survival with Immediate therapy and Observation groups. The graph indicates a statistically significant difference with P=0.02.]

**No. at Risk**

- Immediate therapy: 47, 47, 40, 8
- Observation: 51, 49, 37, 5
Conclusions

Early hormone therapy provides a progression and survival advantage for patients with metastatic prostate cancer.

Critique of ECOG Study

- Powered for 204 patients but closed after 98
- 37/51 men in observation group received hormonal intervention…really a comparison of early vs. late therapy?
- Median PSA at the start of tx in the observation group was 14
- Gleason score not predictive of survival in entire cohort (no central path review)
- Delayed therapy cohorts of men who underwent RRP with + nodes in series from Johns Hopkins, UCLA and Mayo did significantly better than in ECOG study
Biclutamide Monotherapy

• 3 randomized, placebo-controlled, double blind studies

• Efficacy of biclutamide (Casodex) alone as immediate therapy in men with localized or locally advanced CaP or as adjuvant to treatment of curative intent

• 150mg biclutamide qday vs placebo

• Data now available for 8,113 men with 3 year median follow-up

Biclutamide Monotherapy

- 42% reduction in objective disease progression (bone scan) in biclutamide group
- 33% reduction in incidence of bone mets
- 59% reduction in PSA progression
- Trial 23 (North America) failed to show a difference in objective disease progression
- No survival benefit noted yet with short follow-up
Biclutamide Monotherapy

- 25.8% of men in biclutamide group withdrew due to side effects
- Gynecomastia and breast tenderness most common
Rising PSA: Early Hormonal Therapy

• If we believe that a majority of men with PSA-only recurrence actually have occult D1/D2 disease, then early traditional hormonal therapy should provide a disease-specific survival advantage

• Implications from ECOG D1 trial*

Rising PSA: Conclusions

• Rising PSA after surgery is a difficult and not uncommon problem

• The definition of a rising PSA varies
  – PSA > 0.4 ng/mL after RRP
  – Three consecutive rises after nadir for XRT
  – Three consecutive rises above 0.2 ng/mL for brachytherapy
Rising PSA: Conclusions

- No study consistently differentiates local versus metastatic disease
  - Clinical factors help predict
  - Radiologic studies help predict

- From studies of adjuvant therapy, most PSA recurrences seem to represent metastatic disease
Rising PSA: Conclusions

- Early hormonal therapy provides a progression advantage and probably a survival advantage for metastatic prostate cancer

- Hormone therapy in addition to radiation therapy provides a survival advantage
Failure of First Line Salvage Therapy

• Consider addition of anti-androgen

• If on complete androgen blockade—withdraw anti-androgen—1/3 will respond with decline in PSA lasting 4-6 months

• Second line hormonal agents—ketoconazole, megestrol, glucocorticoids, cytotoxic chemotherapy
Rising PSA: Conclusions

- No standard of care for treatment

- Trials may help answer questions and identify agents which provide a definite survival advantage